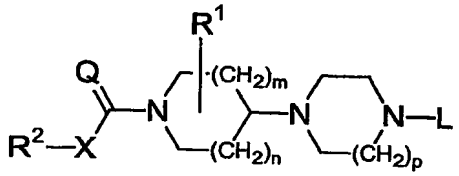
Claims

1. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredients, an opioid analgesic and a therapeutically effective amount of a compound according to Formula (I)



(I)

the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and the prodrugs thereof, wherein

n is 0, 1 or 2;

m is 1 or 2, provided that if m is 2, then n is 1;

p is 1 or 2;

=Q is =O or $=NR^3$;

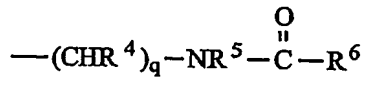
X is a covalent bond or a bivalent radical of formula -O-, -S-, $-NR^3-$;

R^1 is Ar^1, Ar^1C_{1-6}alkyl or di(Ar^1)C_{1-6}alkyl, wherein each C_{1-6}alkyl group is optionally substituted with hydroxy, C_{1-4}alkyloxy, oxo or a ketalized oxo substituent of formula $-O-CH_2-CH_2-O-$ or $-O-CH_2-CH_2-CH_2-O-$;

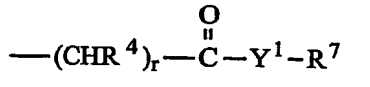
R^2 is Ar^2, Ar^2C_{1-6}alkyl, Het^1 or Het^1C_{1-6}alkyl;

R^3 is hydrogen or C_{1-6}alkyl;

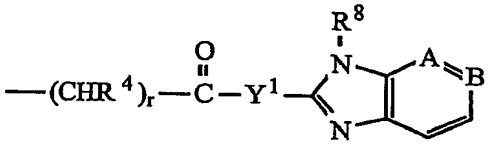
L is hydrogen; Ar^3; C_{1-6}alkyl; C_{1-6}alkyl substituted with 1 or 2 substituents selected from hydroxy, C_{1-6}alkyloxy, Ar^3, Ar^3C_{1-6}alkyloxy and Het^2; C_{3-6}alkenyl; Ar^3C_{3-6}alkenyl; di(Ar^3)C_{3-6}alkenyl or a radical of formula



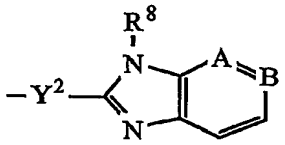
(a-1);



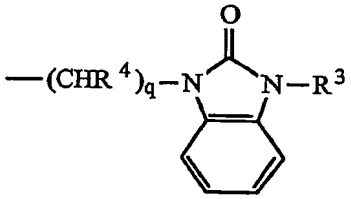
(a-2);



(a-3);



(a-4); or



(a-5);

wherein

each q independently is 2, 3 or 4;

each r is 0, 1, 2, 3 or 4;

each Y^1 independently is a covalent bond, -O- or NR^3;

Y^2 is a covalent bond, C_{1-4}alkanediyl or -C_{1-4}alkylNR^3-;

each -A=B- independently is a bivalent radical of formula -CH=CH-, -N=CH- or -CH=N-;

each R^4 independently is hydrogen, C_{1-6}alkyl, Ar^2 or Ar^2C_{1-6}alkyl;

R^5 is hydrogen, C_{1-6}alkyl or Ar^3;

R^6 is C_{1-6}alkyl, Ar^3, Ar^3C_{1-6}alkyl, di(Ar^3)C_{1-6}alkyl, Ar^3C_{3-7}cycloalkyl, or indolyl;

R^7 is Ar^3; Ar^3C_{1-6}alkyl; di(Ar^3)C_{1-6}alkyl; C_{1-6}alkyl; C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with Ar^3; oxazolyl; oxazolyl substituted with halo or C_{1-6}alkyl; thiazolyl; thiazolyl substituted with halo or C_{1-6}alkyl; imidazolyl; imidazolyl substituted with Ar^3, C_{1-6}alkyl, Ar^3C_{1-6}alkyl or halo; indolinyl; indolinyl substituted with C_{1-4}alkyl; 2,3,4-trihydroquinolinyl; pyrrolidinyl or furanyl;

each R^8 independently is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl or a radical of formula of formula

-Alk-R^{11} (b-1) or

-Alk-Z-R^{12} (b-2);

wherein

Alk is C_{1-6}alkanediyl;

Z is a bivalent radical of formula -O-, -S- or -NR^3-;

R^{11} is phenyl; phenyl substituted with 1 or 2 substituents selected from halo, C_{1-6}alkyl or C_{1-6}alkyloxy; furanyl; furanyl substituted with 1 or 2 substituents selected from C_{1-6}alkyl or hydroxyC_{1-6}alkyl; thienyl; thienyl substituted with 1 or 2 substituents selected from halo or C_{1-6}alkyl; oxazolyl; oxazolyl substituted with 1 or 2 C_{1-6}alkyl substituents; thiazolyl; thiazolyl substituted with 1 or 2 C_{1-6}alkyl substituents; pyridinyl or pyridinyl substituted with 1 or 2 C_{1-6}alkyl substituents;

R^{12} is C_{1-6}alkyl or C_{1-6}alkyl substituted with hydroxy, carboxyl or C_{1-6}alkyloxycarbonyl;

Ar^1 is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C_{1-4}alkyl, haloC_{1-4}alkyl, cyano, aminocarbonyl, C_{1-4}alkyloxy or haloC_{1-4}alkyloxy;

Ar^2 is naphtalenyl; phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from hydroxy, halo, cyano, nitro, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkyloxy, haloC_{1-4}alkyloxy, carboxyl, C_{1-4}alkyloxycarbonyl, aminocarbonyl and mono- or di(C_{1-4}alkyl)aminocarbonyl;

Ar^3 is phenyl or phenyl substituted with 1, 2 or 3 substituents selected from halo, hydroxy, amino, nitro, aminocarbonyl, C_{1-6}alkyl, haloC_{1-6}alkyl or C_{1-6}alkyloxy;

Het^1 is a monocyclic heterocycle selected from pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl; or a bicyclic heterocycle selected from quinolinyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl and benzothienyl; each monocyclic and bicyclic heterocycle may optionally be substituted on a carbon atom by 1 or 2 substituents selected from halo, C_{1-4}alkyl or mono-, di- or tri(halo)methyl; and

Het^2 is a heterocycle selected from 1,4-dihydro-5-oxo-tetrazol-1-yl, imidazo[1,2-a]-pyridinyl, oxazolyl or imidazolyl; each of said heterocycles may be substituted with 1 or where possible 2 substituents selected from C_{1-4}alkyl and Ar^3.

2. A pharmaceutical composition according to claim 1, characterized in that L is hydrogen; C_{1-6}alkyl; C_{1-6}alkyl substituted with hydroxy; C_{3-6}alkenyl; Ar^3; Ar^3C_{1-6}alkyl; di(Ar^3)C_{1-6}alkyl; Ar^3C_{3-6}alkenyl; di(Ar^3)C_{1-6}alkenyl; or a radical of formula (a-1), (a-2), (a-4) or (a-5) wherein :

R^7 is Ar^3; Ar^3C_{1-6}alkyl; di(Ar^3)C_{1-6}alkyl; C_{1-6}alkyl; C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with Ar^3; oxazolyl; oxazolyl substituted with halo or C_{1-6}alkyl; thiazolyl; thiazolyl substituted with halo or C_{1-6}alkyl; imidazolyl; imidazolyl substituted with Ar^3, C_{1-6}alkyl, Ar^3C_{1-6}alkyl or halo; pyrrolidinyl or furanyl;

Ar^3 is is phenyl or phenyl substituted with 1, 2 or 3 substituents selected from halo, hydroxy, amino, aminocarbonyl, C_{1-6}alkyl, haloC_{1-6}alkyl or C_{1-6}alkyloxy;

Het^1 is a monocyclic heterocycle selected from pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl; or a bicyclic heterocycle selected from quinolinyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl and benzothienyl; each monocyclic and bicyclic heterocycle may optionally be substituted on a carbon atom by 1 or 2 substituents selected from halo, C_{1-4}alkyl or mono-, di- or tri(halo)methyl.

3. A pharmaceutical composition according to any one of claims 1 to 2, characterized in that R^1 is Ar^1methyl and attached to the 2-position or R^1 is Ar^1 and attached to the 3-position.

4. A pharmaceutical composition according to any one of claims 1 to 3, characterized in that the R^2-X-C(=Q)- moiety is 3,5-di-(trifluoromethyl) phenylcarbonyl.

5. A pharmaceutical composition according to any one of claims 1 to 4, characterized in that R^1 is Ar^1C_{1-6}alkyl, R^2 is phenyl substituted with 2 substituents selected from methyl and trifluoromethyl, X is a covalent bond and =Q is =O.

6. A pharmaceutical composition according to any one of claims 1 to 5, characterized in that n and m are 1 and p is 1 or 2.

7. A pharmaceutical composition according to any one of claims 1 to 6, characterized in that R^1 is phenylmethyl; R^2 is phenyl substituted with 2 substituents selected from methyl or trifluoromethyl; n, m and p are 1; X is a covalent bond; and =Q is =O.

8. A pharmaceutical composition according to any one of claims 1 to 7, characterized in that L is a radical of formula (a-2) wherein R^4 is hydrogen or phenyl; r is 0 or 1; Y^1 is a covalent bond, -O- or -NH-; R^7 is pyrrolidinyl; furanyl; 1-phenylcyclohexanyl; diphenylmethyl; or phenyl substituted with 1, 2 or 3 substituents each independently selected from methyl, methoxy or chloro

9. A pharmaceutical composition according to any one of claims 1 to 8, characterized in that the pharmaceutical composition comprises a compound selected from the group of:

- 4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-*N*-(2,6-dimethylphenyl)-1-piperazine acetamide;
- 4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-*N*-(1-phenylcyclohexyl)-1-piperazine acetamide;
- 1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-[4-[α-(1-pyrrolidinylcarbonyl)benzyl]-1-piperazinyl]piperidine;
- 1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-[1-[(2-methyl-5-oxazolyl)methyl]-1*H*-benzimidazol-2-yl]-1-piperazinyl]-2-(phenylmethyl)piperidine;
- 4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(4-trifluoromethylphenyl)methyl]-4-piperidinyl]-*N*-(2,6-dimethylphenyl)-1-piperazine acetamide; and
- 4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(3,4-dichlorophenyl)methyl]-4-piperidinyl]-*N*-(2,6-dimethylphenyl)-1-piperazine acetamide.

10. A pharmaceutical composition according to any one of claims 1 to 8, characterized in that the pharmaceutical composition comprises a compound selected from the group of:

- (+)-(B)-*trans*-4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-*N*-(2,6-dimethylphenyl)-1-piperazine acetamide;
- (-)-(B)-*cis*-4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-*N*-(2,6-dimethylphenyl)-1-piperazine acetamide; and
- (+)-(B)-*trans*-4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-*N*-(2,6-dimethylphenyl)-1-piperazine acetamide (L)-malic acid (1:1).

11. A pharmaceutical composition according to any one of claims 1 to 6, characterized in that it is formulated for simultaneous, separate or sequential use.

12. A pharmaceutical composition according to any of claims 1 to 11, characterized in that the opioid analgesic is one or more compounds selected from the group of alfentanil, buprenorphine, butorphanol, carfentanyl, codeine, diacetylmorphine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, lofentanyl, meperidine, methadone, morphine, nalbuphine, oxycodone, oxymorphone, pentazocine, propoxyphene, remifentanyl and sufentanyl; and derivatives and pharmaceutical acceptable salts thereof.

13. A pharmaceutical composition according to claim 12 characterized in that the opioid analgesic is one or more compounds selected from the group of oxycodone, codeine, morphine, fentanyl, buprenorphine, hydrocodone, hydromorphone and pharmaceutical acceptable salts and derivatives thereof.

14. A pharmaceutical composition according to any one of claims 1 to 13, characterized in that it is in a form suitable to be orally administered.

15. The use of a pharmaceutical composition according to any one of claims 1 to 13 for the manufacture of a medicament for the prevention and/or treatment of pain and/or nociception.

16. The use of a pharmaceutical composition according to any one of claims 1 to 13 for the manufacture of a medicament for the prevention and/or treatment of acute and chronic pain, more in particular in inflammatory, post-operative, emergency room (ER), breakthrough, neuropathic and cancer pain treatments.

17. The use of a pharmaceutical composition according to any one of claims 1 to 13 for the manufacture of a medicament for the prevention and/or treatment of emesis in opioid-based treatments of pain.

18. The use of a pharmaceutical composition according to claim 17 for the manufacture of a medicament for the prevention and/or treatment of nausea and vomiting in opioid-based treatments of pain.

19. The use of an NK_1-receptor antagonist, in particular an NK_1-receptor antagonist according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and prodrugs thereof, for the manufacture of a medicament for the prevention and/or treatment of respiratory depression in opioid-based treatments of pain.

20. The use of an NK_1-receptor antagonist, in particular an NK_1-receptor antagonist according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and prodrugs thereof, for the manufacture of a medicament for reducing and/or overcoming the tolerance observed with opioids in opioid-based treatments of pain.